

Lack of effect of H₂-receptor antagonists and antacids on the gastric and duodenal gastrin-, somatostatin- and serotonin-producing cells in patients with acid peptic disorders

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WR YACOUB, ABR THOMSON, P HOOPER, LD JEWELL. Lack of effect of H₂-receptor antagonists and antacids on the gastric and duodenal gastrin-, somatostatin- and serotonin-producing cells in patients with acid peptic disorders. *Can J Gastroenterol* 1996;10(4):255-259. Standard therapeutic approaches to acid peptic disorders have dealt with neutralizing or inhibiting aggressive factors and/or bolstering defensive factors. Gastric and duodenal mucosal biopsies were examined from 90 patients with various acid peptic disorders, as follows: reflux esophagitis (n=24), gastric ulcer (n=13), duodenal ulcer (n=47) and nonulcer dyspepsia (n=6). Seven patients with minimal dyspeptic symptoms and an endoscopically and histologically normal stomach and duodenum served as controls. Immunoperoxidase staining for gastrin-producing G cells, somatostatin-producing D cells and serotonin-producing EC cells was carried out on fundic, antral and duodenal biopsies, and quantitated using a Zeiss MOP videoplan. No significant effects secondary to treatment with antacid, ranitidine or cimetidine were observed on endocrine cell densities and ratios. Biopsies obtained on different occasions over time indicated that in patients on enprostil (a synthetic E₂ prostaglandin), there was a trend towards increasing cell counts, suggesting that the serum gastrin-lowering effect of this drug may result from inhibition of

gastrin release. Thus, H₂-receptor antagonists and antacids do not alter gastric or duodenal mucosal G, D or EC cells in patients with acid peptic disorders.

Key Words: Antacids, Cimetidine, D cells, EC cells, Enprostil, G cells, Ranitidine

Inefficacité des anti-H₂ et des anti-acides sur les cellules gastriques et duodénales productrices de gastrine, de somatostatine et de sérotonine chez des patients atteints de troubles peptiques dus à l'acidité

RÉSUMÉ : Les approches thérapeutiques classiques actuelles face aux troubles peptiques dus à l'acidité visent en général à neutraliser ou à inhiber les facteurs agresseurs ou à stimuler les facteurs protecteurs. Des biopsies des muqueuses gastrique et duodénales provenant de 90 patients souffrant de divers troubles peptiques dus à l'acidité ont été examinées. La répartition était la suivante : œsophagite de reflux (n=24), ulcère gastrique (n=13), ulcère duodé-

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nal (n=47) et dyspepsie non ulcéreuse (n=6). Sept patients présentant des symptômes dyspeptiques minimes et dont l'estomac et le duodénum étaient normaux à l'endoscopie et à l'examen histologique ont servi de témoins. Des tests de coloration à l'immunoperoxydase ont été effectués pour dépister la présence de cellules G productrices de gastrine, de cellules D productrices de somatostatine et de cellules EC productrices de sérotonine sur des tissus du fundus, de l'antrum et du duodénum, qui ont été quantifiées à l'aide du vidéoplan Zeiss MOP (CarlZeiss, Allemagne). Le traitement aux anti-acides, à la ranitidine ou à la cimétidine n'a

entraîné aucun effet secondaire significatif sur les densités et les ratios de cellules endocriniennes. Les biopsies obtenues en diverses occasions au cours d'une période donnée ont révélé que chez les patients sous enprostil (une prostaglandine E₂ synthétique), on notait une tendance à des numérations cellulaires accrues, laissant supposer que l'effet à la baisse de ce médicament sur les taux sériques de gastrine pourrait résulter d'une inhibition de la libération de gastrine. Ainsi, les anti-H₂ et les anti-acides ne modifient pas les cellules G, D ou EC des muqueuses gastrique ou duodénale chez les patients atteints de troubles peptiques dus à l'acidité.

Standard therapeutic approaches to ulcer disease deal with aggressive factors, such as acid and pepsin, either by neutralizing or inhibiting them (1-5), or by bolstering defensive factors (6). Prostaglandins have been claimed to strengthen the natural defence of the gastric mucosa (7). Enprostil, a synthetic prostaglandin E₂, is the only drug reported to lower serum gastrin concentrations (8-12) and reduce G cell hyperplasia in patients with duodenal ulcer disease (13). In the present investigations, we examined the influence of various therapeutic regimens on the number and ratios of the gastrin-producing G cells, somatostatin-producing D cells and serotonin-producing EC cells in the stomach and duodenum of patients with acid peptic disorders.

PATIENTS AND MATERIALS

Patient characteristics: Mucosal biopsy specimens were obtained from the gastric antrum, body and fundus, descending duodenum and duodenal bulb of 97 patients. The study groups comprised 47 patients with endoscopically demonstrated duodenal ulcer disease (DU); 13 with gastric ulcers (GU); 24 with esophagitis due to gastroesophageal reflux disease (GERD); six with nonulcer dyspepsia (NUD), ie, patients having symptoms suggestive of ulcer disease in whom endoscopic and histological examinations revealed gastritis and/or duodenitis without ulceration; and seven with various gastrointestinal disorders (eg, Crohn's disease, irritable colon) and minimal dyspeptic symptoms in whom endoscopic and histological examinations revealed normal gastric duodenum. Table 1 lists the various treatment regimens patients were on at the time of biopsy, and the number of patients in each therapeutic subgroup. In 24 patients (two with NUD, 11 with DU, seven with GU and four with GERD) mucosal biopsies were obtained on more than one occasion. This allowed examination of the effect of various therapeutic agents on the endocrine cell densities over time, bringing the total number of examined biopsy specimens to 144. Cell counts carried out in biopsies obtained from patients on enprostil alone were combined with those on enprostil plus ranitidine. Only biopsies obtained from patients on the following regimens were included in the statistical analysis: no treatment, antacid, ranitidine, cimetidine, or enprostil plus ranitidine.

Immunocytochemical identification of the three endocrine cell types (gastrin-producing G cells, somatostatin-

TABLE 1
Treatment regimens that patients were on at biopsy

n	Treatment regimen
22	No treatment
14	Antacid (Gelusil [Warner Wellcome] 10 to 20 mL or 2 to 4 tablets between meals and at bedtime; Maalox [Ciba-Geigy Canada Ltd] 10 to 29 mL or 1 to 2 tablets tid and at bedtime)
34	Ranitidine (150 mg bid or tid), with or without antacid
14	Cimetidine (300 mg bid or qid, or 600 mg bid) with or without antacid
6	Enprostil (35 µg bid) plus ranitidine, with or without antacid
1	Misoprostol (200 µg bid)
1	Enprostil plus sucralfate (1 g qid)
1	Ranitidine plus sucralfate
3	Enprostil (35 to 105 µg/day)
1	Sucralfate plus antacid

producing D cells and serotonin-producing EC cells) in the gastric and duodenal biopsies was achieved using the peroxidase antiperoxidase technique of Sternberger (14). Morphometric quantitative studies of these endocrine cells were objectively performed using the Zeiss MOP videoplan computerized image analysis system (Carl Zeiss, Germany). Details of the immunocytochemical and morphometric studies were described elsewhere (15).

Statistical analysis: All analyses were based on the square roots of the cell counts. A theoretical argument suggested that on this scale the variance would remain nearly constant as the mean changed. Plots of the data showed that the distributions of the root counts were fairly symmetric.

How the G, D and EC square root counts and their ratios varied among the six different sites for each treatment regimen was examined. Point estimates were examined and tests of significance were carried out. Paired *t* tests for differences in the root counts and Wilcoxon signed-rank tests for differences in the ratios were used. The nonparametric test was used in the latter instance because the distribution of the ratios appeared highly skewed. Multivariate analysis of covariance was done to examine whether the mean root counts for the G, D and EC cells in the six sites depended on the treat-

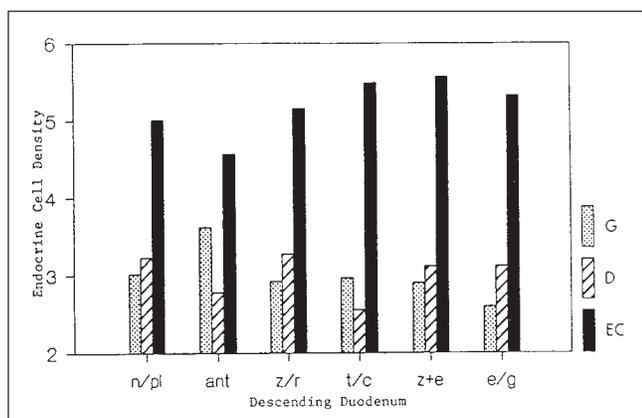


Figure 1) Treatment effect on G, D and EC cell densities of various treatment groups in the descending duodenum. No differences are discerned. ant Antacid group; D D cells; EC EC cells; e/g Enprostil group; G G cells; n/pl No therapy or placebo; t/c Cimetidine group; z+e Ranitidine and enprostil group; z/r Ranitidine group

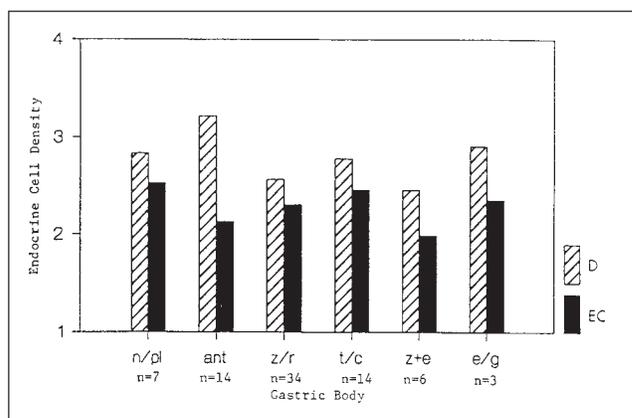


Figure 4) Treatment effect on G, D and EC cell densities of various treatment groups in the gastric body. No differences are discerned. ant Antacid group; D D cells; EC EC cells; e/g Enprostil group; n/pl No therapy or placebo; t/c Cimetidine group; z+e Ranitidine and enprostil group; z/r Ranitidine group

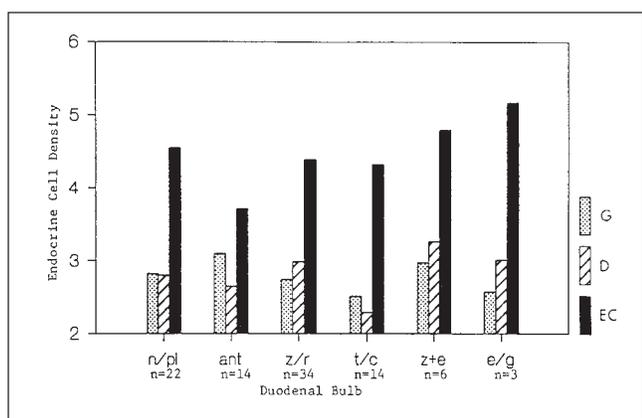


Figure 2) Treatment effect on G, D and EC cell densities of various treatment groups in the duodenal bulb. No differences are discerned. ant Antacid group; D D cells; EC EC cells; e/g Enprostil group; G G cells; n/pl No therapy or placebo; t/c Cimetidine group; z+e Ranitidine and enprostil group; z/r Ranitidine group

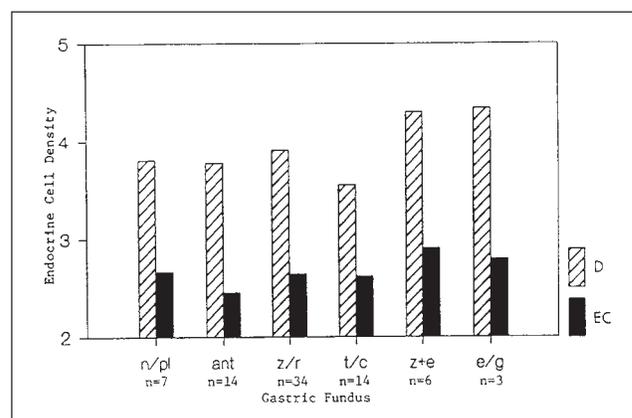


Figure 5) Treatment effect on G, D and EC cell densities of various treatment groups in the gastric fundus. No differences are discerned. ant Antacid group; D D cells; EC EC cells; e/g Enprostil group; n/pl No therapy or placebo; t/c Cimetidine group; z+e Ranitidine and enprostil group; z/r Ranitidine group

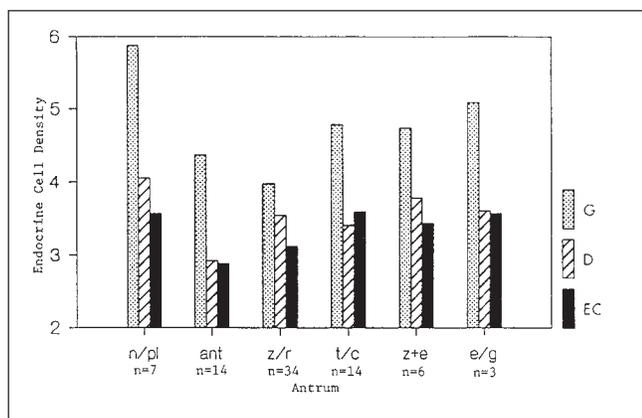


Figure 3) Treatment effect on G, D and EC cell densities of various treatment groups in the gastric body. No differences are discerned. ant Antacid group; D D cells; EC EC cells; e/g Enprostil group; G G cells; n/pl No therapy or placebo; t/c Cimetidine group; z+e Ranitidine and enprostil group; z/r Ranitidine group

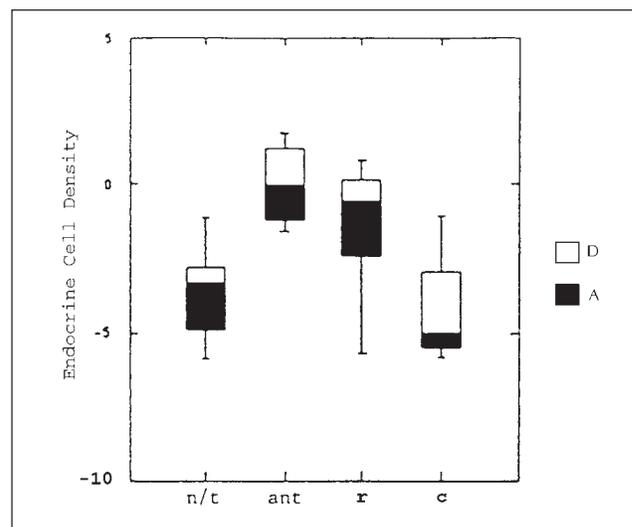


Figure 6) Treatment effect on G cells in gastroesophageal reflux disease patients. A trend to increasing duodenal G cells (D) and diminishing antral G cells (A) is seen. ant Antacid; c Cimetidine; n/t No therapy; r Ranitidine

TABLE 2
Effect of various therapeutic regimens* on various cell ratios

Ratio	Site	Regimen				
		No therapy (n=22)	Antacids (n=13)	Ranitidine ± antacid (n=34)	Cimetidine ± antacid (n=14)	Ranitidine ± enprostil ± antacid (n=6)
G:D	Descending duodenum	0.831	1.2878	0.862	1.129	0.968
	Duodenal bulb	0.905	1.127	0.923	1.084	0.897
	Antrum	1.553	1.453	1.165	1.555	0.975
G:EC	Descending duodenum	0.587	0.739	0.527	0.614	0.637
	Duodenal bulb	0.611	0.802	0.541	0.588	0.572
	Antrum	1.760	1.520	1.317	1.403	1.319
D:EC	Descending duodenum	0.522	0.653	0.628	0.505	0.616
	Duodenal bulb	0.620	0.678	0.693	0.659	0.774
	Antrum	1.329	1.038	1.140	0.899	0.982
	Body	1.183	1.434	1.54	1.265	1.219
	Fundus	1.459	1.504	1.425	1.347	1.583

*Irrespective of the primary diagnosis

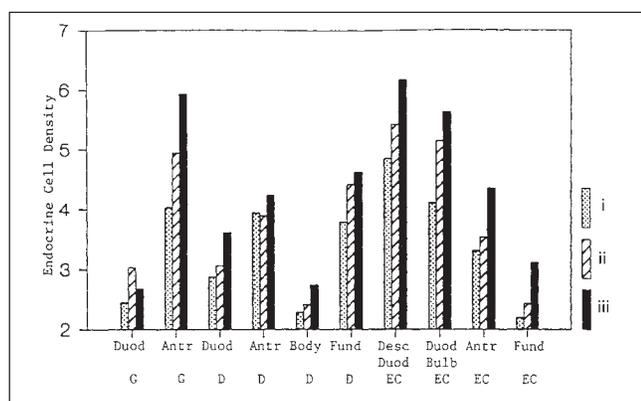


Figure 7) Effect of enprostil over time. There is an apparent trend to increasing G cells (G) over time. Antr Antrum; DD cells; Desc Descending; Duod Duodenum; EC EC cells; Fund Fundus; i First biopsy; ii Second biopsy; iii Third biopsy

ment regimen. The authors considered an additive model and found no significant effects.

The paired samples *t* test was used to investigate cell density differences over time in biopsies obtained from patients on enprostil.

RESULTS

Effects of various therapeutic agents on G, D and EC cells and their ratios: There was no treatment effect on the mean G, D and EC cell densities in the various patient groups (Figures 1-5) except for GERD patients (Figure 6). Biopsies obtained from seven GERD patients who were not receiving treatment demonstrated fewer duodenal versus antral G cells. In four GERD patients on antacid, seven on ranitidine with/without antacid and four on cimetidine with/without antacid, the difference was reduced by virtue of increased G cell counts in the duodenum.

There was also no effect on the gastrin and duodenal G:D, G:EC and D:EC cell ratios attributable to the various therapeutic agents (Table 2).

Effect of enprostil on G, D and EC cell densities in biopsies

taken over time: The effect of enprostil on the G, D and EC cell densities was examined in 17 patients (eight with DU, six with GU, two with GERD and one with NUD). Three biopsies were obtained from each patient over six to 12 months. At the initial biopsy, three patients were on cimetidine with/without antacid, three were on ranitidine plus enprostil with/without antacid and nine were on antacid (two other patients were on no treatment). The results of the analysis (paired samples *t* test) indicated increases ($P < 0.1$) in the values of the mean G, D and EC cell densities in the various sites (Figure 7). Comparing cell densities in the third biopsies with those in the initial ones, significant increases were found in the antral G cell densities ($P = 0.03$), duodenal D cell densities ($P = 0.038$), descending duodenal and duodenal bulb EC cell densities (respective *P* values 0.015 and 0.007), antral EC cell densities ($P = 0.048$) and gastric body and fundic EC cell densities ($P = 0.001$).

DISCUSSION

While overall there was no evidence that the various therapeutic agents had any significant effect on the three endocrine cell densities in all patient groups, there appeared to be an unanticipated exception for GERD patients. In GERD patients on no therapy, gastric and duodenal G cell densities were similar to those of 'controls' (patients with various gastrointestinal disorders and minimal dyspeptic symptoms), with fewer G cells in the duodenum than in the antrum. GERD patients on antacid or cimetidine with/without antacid therapy exhibited increased duodenal G cell densities. Great caution must be exercised in the interpretation of this finding due to great interindividual variability in cell densities and the small number of observations in the treatment subgroups of GERD patients.

The reported lack of effect of H_2 blockers on endocrine cells is in agreement with Ribet and co-workers (16) who found no changes in antral G cells and a doubtful increase in antral D cells in patients treated with ranitidine. That study

also confirms the absence of an effect of cimetidine as reported by Gutierrez et al (17) and Arnold et al (18).

Furthermore, treatment appears to exert no significant effect over duodenal G:D, gastric (body and fundus) and duodenal G:EC and D:EC ratios. This suggests that possible drug-induced alterations in peptide and amine secretions in some patients with peptic disorders are not associated with or attributed to cell ratio variation.

Enprostil, which is a synthetic prostaglandin E₂, has the unique effect of lowering basal and postprandial serum gastrin concentration (8-12), and reducing both gastrin 17 and gastrin 34.

Enprostil has been reported to be effective and safe in healing duodenal and gastric ulcers (9,19-27). The effect of enprostil on endocrine cell densities has been investigated in multiple biopsies obtained from 17 patients over periods of up to a year. There was a trend for increasing G, D and EC

cell densities over time in the duodenal and gastric sites, particularly when comparing the third with the initial biopsies. The finding is in agreement with the serum gastrin lowering effect of enprostil (8,10). This effect on serum gastrin concentrations may be the result of an inhibition of gastrin release from G cells.

CONCLUSIONS

Immunocytochemical identification and objective morphometric quantification of gastric and duodenal G, D and EC cells have been successfully achieved using the peroxidase antiperoxidase technique of Sternberger (14) and the Zeiss MOP videoplan computerized analysis system. Biopsies obtained over time indicated that in patients treated with enprostil there was a trend towards increasing cell counts, suggesting the serum gastrin lowering effect of this drug may result from inhibition of gastrin release.

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